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Letters to the Editor

Do drugs that stimulate ovulation increase the risk for endometrial stromal sarcoma?

Sir,

We read with interest the epidemiological study by Brinton *et al.* (2004), which reports a statistically significant risk for invasive breast cancers after clomiphene citrate treatment. Overall reports on the pathogenetic influence of infertility treatment on breast cancer risk are conflicting (Gauthier *et al.*, 2004). We report our data on ovulation-stimulating drugs in women with endometrial stromal sarcoma (ESS), a hormone-sensitive tumor of young women that accounts for $<0.2\%$ of gynaecological malignancies. The great majority of ESS express estrogen receptors, progesterone receptors, gonadotropin-releasing-hormone receptors, and aromatase (Reich and Regauler, 2000, 2004a,b). Among 64 patients with ESS who we are studying, eight (12.5%) had undergone *in vitro* fertilization treatment including clomiphene. To our knowledge this is the first such observation in a large patient group with ESS.

We would like bring attention to a possible association between the treatment with clomiphene citrate and the development of ESS. This is potentially important because patients with ESS are premenopausal, have an incidence of concomitant breast cancer, and often have a family history of hormone-sensitive cancers (personal observation). We speculate that some of these patients may be carriers of a genetic abnormality which influences endocrine signalling, as described for familial breast and prostate cancer. Such carriers would be at an increased risk of hormone-dependent neoplasms during or after treatment with ovulation-stimulating drugs.

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Reply: Do drugs that stimulate ovulation increase the risk for endometrial stromal sarcoma?

Sir,

Reich and Regauer (2004) have made an intriguing observation regarding a preponderance of histories of *in vitro* fertilization among patients developing endometrial stromal sarcomas (ESS). Although the absence of information as to how long these patients were followed or what types and dosages of drugs they received limits the extent to which a biological connection can be made, we agree that the effects of fertility drugs on uterine cancers is an issue that deserves further pursuit, particularly given the well-recognized role of hormonal factors in the etiology of these tumors. Clomiphene is of particular interest, given that it is a selective estrogen receptor modulator (SERM), structurally similar to tamoxifen, a drug which has been linked with >2-fold increases in the risk of uterine cancers and even higher risks for certain rare tumor histologies (Curtis *et al.*, 2004). Of note in this regard are several reports of ESS among tamoxifen-treated women (Liao and Lin, 2001; Saga *et al.*, 2003).

Despite biological plausibility, few previous investigations have assessed the effects of usage of fertility drugs on the risk of uterine cancers. One previous study in Israel noted a 2-fold increased risk of endometrial cancer among women exposed to fertility drugs, although based on only 21 cancers (Modan *et al.*, 1998). In our cohort study of infertile women, from which we recently reported results regarding breast cancer risk (Brinton *et al.*, 2004), we also found an $\sim$2-fold increased risk of uterine cancers associated with clomiphene use, with even further elevations in risk among women with higher doses or those followed for longer periods of time (Althuis *et al.*, in press). However, of the 39 observed uterine carcinomas, we did not observe any ESS, with the majority of cancers for which we were able to derive pathological details reflecting the more common diagnosis of endometrial adenocarcinoma.

Although the rate reported by Reich and Regauer (2004) of 12.5% of previous *in vitro* fertilization among women with ESS appears high, a contributing factor may be that ESS often arise among patients with endometriosis (Corpa *et al.*, 2004), who would be at high risk of being infertile. Clarification of the true nature of a relationship between fertility treatment and ESS would require use of appropriate comparison groups and adequate adjustment for other predictors of risk. However, as emphasized by the absence of any ESS in our investigation of $>12\,000$ women, this will be an extremely difficult issue to study in cohort studies. Assembling a large series of cancers for a case-control study will also be difficult, given that ESS is an extremely rare tumor, having an incidence rate among females during the period 1992–2001 in the US of 0.34 per 100 000 women [Surveillance,

Epidemiology and End Results (SEER) Program SEER & Stat Database].

We agree that effects of ovulation induction should continue to be investigated for a variety of cancers. However, in order for results not to cause unnecessary alarm, it is important that they be carefully communicated. We therefore caution against our findings for breast cancer being communicated as a significant increase, since the only statistically significant increase pertained to a relatively small subgroup, namely clomiphene users who developed invasive cancers after 20 or more years of follow-up (Brinton *et al.*, 2004). The results, however, support the need for further evaluation of long-term effects of fertility drugs.

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Hysterectomy and bilateral oophorectomy for severe premenstrual syndrome

Sir,

A curious coincidence: the publication of the paper by Cronje *et al.* (2004) on hysterectomy and bilateral oophorectomy for severe premenstrual syndrome and the death of Katharina Dalton (1916–2004), a pioneer and populariser of the 'illness' PMS on September 17 in Britain. In O'Connor's obituary in the New York Times of 28 September, Dr Shangold, a gynaecologist is quoted as saying 'Many people did not believe it was a real entity'. She continued: 'She really brought it into the public eye, and eventually it became an accepted disorder for which we now have good treatments'. She did not elaborate on these treatments, of which I am not aware at all, but I certainly do not think that the treatment as proposed by Cronje *et al.* could qualify in this respect.

I really thought that the old times in which women with psychiatric symptoms were operated upon by gynaecologists was long behind us, but I am wrong. In a retrospectively mortifying period in the history of our profession, from about the 1870s until 1910, many women were castrated by the so-called 'normal ovariotomy', which was called Battey's operation by J.Sims, as others underwent clitoridectomies for 'nymphomania'. In Europe the German gynaecologist Hegar performed many of these operations, while in the US this role was performed by Battey. The details of this history can be found in the instructive chapter 'Gynaecological Surgery and the Desire for an Operation' in Shorters excellent book (1992) on the history of psychosomatic illness.

We think that PMS is a psychosomatic illness in which the contribution of abnormal ovarian function has never been proven. Since 1983 it is called 'Late luteal dysphoric disorder' in the Diagnostic and Statistical Manual of Mental Disorders (DSM). It is there that it belongs, and not in books on gynaecologic surgery. Treatment for this type of functional syndrome should be along psychosocial lines and not even the most severe symptoms should be taken as an indication for the removal of healthy organs.

In this kind of illness (cf Charcot's grande hysterie, chronic fatigue syndrome, postnatal depression, post-whiplash syndrome etc.) there is a striking contrast between the extreme visibility of the symptoms and the lack of objective findings. Although this category of patients do seek a medical solution for their problems, doctors should refrain from medical treatments, as the problem is incurable with conventional medical modalities such as surgery or medicines.

The apparently successful and sustained cures of PMS by hysterectomy and oophorectomy, as reported by Cronje *et al.* (2004) can be explained in other ways. It is well known that surgery does have strong placebo effects (Johnson, 1994) and the PMS sufferer initially gets all the rewards that a sickness role in our society provokes. After recovering from surgery these women are converted into 'chronic patients', depending on hormone replacement therapy and this again will please most of them, because of the prolonged attention this entails. It should be possible to manage these women in other ways and medical treatment—especially surgery—should in my opinion be avoided in all cases.

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